SEMISOLID DOSAGE FORMS

13th week

Preparation methods of semisolids

* Cold preparation (Preparation at room temperature)

* Hot preparation (Preparation by melting)

Cold preparation (Preparation at room temperature)

This method is used;

- When the ingredients are in semisolid or liquid state at room temperature
- When a single-phase semisolid formulation is prepared
- When a lab scale formulation is prepared

✓ Formulation is prepared using mortar and pestle. First the solid particles are milled. Then they are mixed with low viscous excipients in order to provide the homogenous mixing with semisolid base.

Hot preparation (Preparation by melting)

This method is used;

- When the components of base are in solid state at room temperature (waxes, hard paraffin etc)
- When the active substance is soluble in the melting base
- When a multi-phase semisolid formulation is prepared
- When a large scale formulation is prepared

- Emulsions are prepared generally by combining the oil-soluble ingredients (e.g., petrolatum, waxes and fats) and heating the mixture to about 75°C (temperature at which the oil-phase ingredients are molten).
- The water-soluble ingredients are combined separately and heated to slightly above 75°C.
- The aqueous phase then is added to the oil phase slowly and with constant agitation.
- When the emulsion is formed, the mixture is allowed to cool maintaining slow agitation.

- At this stage the active substances which has been milled to reduce any particle aggregates are added.
- Volatile or aromatic substances are generally added when the finished emulsion has cooled to about 35°C.
- At this point, additional water can be added to compensate for any evaporative losses because of the higher temperatures in emulsion formation process.

Controls for semisolid dosage forms

- Homogenity control
- Physical controls
- Rheological controls
- pH control
- Assay - Determination of quantity of active substance
- Impurity control
- Weight control
- Microbiological controls
- Antimicrobial preservative content
- Antioxidant content
- Sterility controls
- Stability tests
- In vitro drug release tests
- In vivo studies

Homogenity control

The semisolid preparation is checked for homogeneity (by microscope or inspection)

Physical controls

Existence of odor, colour or viscosity change, rancidity, drying and phase separation in formulation is checked.

Particle contamination

It is important for ophtalmic semisolid formulations.

Eye ointments must not contain metal particles or particles larger than 20 µm.

Assay

A specific and stability-indicating test should be used to determine the strength (content) of the drug in semisolid product.

Impurities

- Process impurities, synthetic by-products and other inorganic-organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product.
- These impurities are controlled by the drug substance and excipients monographs.
- Organic impurities arising from the degradation of the drug substance and those arising during the manufacturing process of the drug product should be monitored.

Rheological controls

Rheological properties of semisolid dosage forms are important in terms of;

- The viscosity of the product
- The ease of use of the product
- The spreadability of the product
- The drug release from the product

* Viscosimeters are used for determining the viscosity of the preparation.

Microbiological controls

- The microorganisms below should not exist in a semisolid formulation intended for cosmetic or therapeutic purposes.
- For this purpose, appropriate antimicrobials should be used at accurate concentrations.

Staphylococcus aureus
Serretia marcescens
Escherichia coli
Acinebacter anitratus
Proteus mirabilis
Pseudomonas species
Candida species
Clebsiella species

The type of microbial tests and acceptance criteria should be determined based on the nature of the drug substance, method of manufacture and the intended use of the drug product.

Antimicrobial Preservative Content

- Acceptance criteria for preservative content in multidose products should be established.
- They should be based on the levels of antimicrobial preservative necessary to maintain the product's microbiological quality at all stages throughout its proposed usage and shelf life.

Antioxidant Content

If antioxidants are present in the semisolid drug product, tests of their content normally should be determined.

Sterility controls

- Depending on the use of the dosage form, e.g., ophtalmic semisolid formulations and burn / wound ointments, sterility of the product should be demonstrated as appropriate.

- They are either prepared aseptically or sterilized after production.

Stability tests

1) Physical stability

2) Chemical stability

3) Microbiological stability

should be investigated during the shelf life of the product.

In vitro release tests

- ✓In vitro release testing is used to monitor the release and diffusion of active substances from semisolid dosage forms and has long been considered a valuable tool in formulation development.
- ✓In vitro release testing is recommended by the United States Food and Drug Administration (FDA) as a measure of "product sameness" during scale up and postapproval changes for semisolids.

The application of in vitro release test has many additional benefits such as;

- Its use in product development
- Identification of critical manufacturing variables
- Estimating in vivo performance
- Product performance assessment including batch–batch and lot–lot uniformity

- ✓Various factors such as the size of the dispersed particles, the interfacial tension between the phases and the rheology of the formulation effect the physical properties of the semisolid dosage form.
- ✓All of these factors have an influence on the release profile of the active ingredient.

- It is important to properly validate a release test before using it for product qualification.
- In vitro release test must be reproducible and reliable.
- Although it is not a measure of bioavailability, the performance test must be capable of detecting changes in drug release characteristics from the finished product.
- Changes in drug release characteristics have the potential to alter the biological performance of the drug in the dosage form.

Changes in drug release feature may be related to;

- ✓Active or inactive ingredients in the formulation
- ✓ Physical or chemical feature of the finished formulation
- ✓ Manufacturing variables
- ✓ Shipping and storage effects
- ✓ Aging effects and other formulation factors that are critical to the quality characteristics of the finished drug product.

Vertical diffusion cell system (Franz diffusion cell)

- ✓The vertical diffusion cell is recommended by the USP.
- ✓This system is one of the more widely accepted apparatuses for in vitro diffusion studies and the most commonly used in vitro model for the study of drug release from topical dosage forms.

- ✓The main advantages of the Franz diffusion cell are its ease of operation and its large sample size, which ensures consistent results.
- ✓Moreover, the technique is simple, reliable, reproducible and suitable for the determination of in vitro release profile of gels, creams and ointments.

- ✓The body of diffusion cell normally is made from borosilicate glass, although different materials may be used to manufacture the body and other parts of the system.
- ✓None of the materials should react with or absorb the test product or samples.

- The Franz diffusion cell assembly consists of two chambers; a donor chamber and a receptor chamber. They are held together by a clamp.
- The receptor chamber orifice should be fabricated to the same size as the donor chamber orifice.

- Donor and receptor chambers are separated from each other by a membrane.
- A layer of the semisolid product is placed in the donor chamber on top of the membrane in contact with the receptor medium which is in the receptor chamber.

Membrane

- Diffusion of active substance from semisolid dosage form to the receptor medium takes place through an inert and permeable membrane.
- The membrane also keeps the product and the receptor medium separate and distinct.
- Franz diffusion cells have been used with different membranes ranging from human and animal skin to synthetic membranes.

Membrane

- The use of skin or synthetic membranes depends on the objective of the test.
- Skin is typically used as a membrane in order to mimic biological conditions whereas synthetic membranes are used to detect differences in batch–batch and lot–lot comparisons.
- Various synthetic membranes have been used such as cellulose acetate/nitrate/mixed ester, polysulfone, polytetrafluoroethylene, nylon, polycarbonate etc..

Receptor Medium

- It is advisable to use a receptor that resembles the physiological condition of the skin.
- The selection of an appropriate receptor medium is very important and depends on the solubility of the active substances.
- The commonly used receptor medium for water soluble drugs are aqueous buffer solutions.
- However, for products formulated with a water insoluble active compound, the selection of an appropriate receptor medium to maintain sink characteristics is a challenge.
- In order to facilitate and monitor drug release from such topical formulations, it may be necessary to alter the receptor fluid's pH, to add surfactants and/or organic solvents.

Receptor Medium

- Alcohol and/or a surfactant may be incorporated into the receptor medium according to the solubility of active substances.
- A further important consideration is the pH of the medium and the choice of pH should be based on the pH-solubility profile of the active substance and the pH of the formulation.
- The selected receptor should permit a sufficient amount of release of active substance within a reasonable period and sink conditions should be maintained.

- ✓The occurrence of air bubbles at the membrane - liquid interface which is often difficult to observe is a serious drawback of vertical diffusion cell system.
- ✓Failure to remove these air bubbles can have serious consequences relating to the precision, accuracy and reproducibility of the resulting data.
- ✓Deaeration of the receptor medium is essential to prevent bubble formation at the membrane – receptor medium interface since it reduces the contact area between the membrane and the receptor liquid.

- ✓The receptor medium should be stirred throughout the experiment at a constant stirring speed usually with a magnetic stirrer.
- ✓Various rates of stirring have been reported between 400 and 800 rpm to ensure uniform mixing of the receptor phase.
- ✓It is suggested that samples should be collected over at least a 6 hours period.
- ✓In order to determine the release profile of an active compound, six samples are recommended.
- ✓Specific volumes of samples are withdrawn from the receptor chamber at predetermined time intervals and replaced with fresh receptor medium.

- ✓The test temperature is usually maintained at 32 ± 1 °C throughout the experiment to reflect normal skin temperature.

Flow through cells (USP Apparatus 4)

- The receptor medium continuously flows through the acceptor compartment and as a result the medium is refreshed continually.
- The apparatus consists of a reservoir with a release medium, a pump and a water bath.
- The pump is used to force the release medium upward through the vertically placed flow through cell.

- In order to measure the release rate of the active compound from a semisolid formulation, an insertion cell is placed inside the flow through cell.
- The dissolution liquid is generally collected in a separate reservoir as it leaves the insertion cell.

Packaging of semisolid preparations

- ✓ Semisolid formulations which are prepared in pharmacies can be packed in glass jars, plastic boxes or tubes.
- ✓ Semisolid formulations which are prepared in industry are packed in metal tubes or plastic tubes.

Storage of semisolid preparations

- ✓ Semisolid preparations should be stored at room temperature unless otherwise specified.

Rx

Salicylic acid		5 g
Cold cream	sq	25 g

Salicylic acid is soluble in;

500 parts of water, 15 parts of boiled water, 2.7 parts of alcohol,

2 parts of ether, 80 parts of olive oil.

Rx

Rivanol		0.3 g
Juniper tar		
Precipitated sulphur	ā.ā.	2.0 g
Salicylic acid		0.5 g
Olive oil		4.0 g
Petrolatum		40.0 g

Rivanol is soluble in 15 parts of water.

Salicylic acid is soluble in 2.7 parts of alcohol.

Rx

Burow solution	10 ml
Petrolatum	40 g
Lanolin /	
Water	ā.ā. 20 g

Rx

Oxygenated water	10 ml
Zinc oxide	2 g
Precipitated sulphur	1.5 g
Anhyrous lanolin	40 g

Rx

Precipitated sulphur		4 g
Simple ointment	sq	50 g